PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent
appln. of : Heng Wang, et al.

Appln. No: 10/566,697

Filed: May 10, 2006

For: **METHOD OF PREPARING EPITOPES CHIMERIC GENE VACCINE**

Confirm No. 9761

Examiner: Teresa D. Wessendorf

Art Unit: 1639

Docket No: 2008-282

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Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Sir:

This reply brief is being submitted electronically on February 22, 2010 in response to the Examiner's Answer dated December 29, 2009.

This reply brief is being timely filed within two months of the Examiner's Answer, pursuant to 37 C.F.R. § 41.41.

I. Rejection Under 35 U.S.C. 112, Second Paragraph

In response to appellants' argument that the Examiner did not provide factual support for her assertion that appellants' use of "type" in claim 20 rendered the claim indefinite, the Examiner acknowledges that each case is to be determined on its own merits, and that the term "type" is defined in the specification and that, as defined in the specification, the term is vague and indefinite. The Examiner also cites Ex parte Copenhaver, 109 U.S.P.Q 118 (Bd. App. 1955) for the proposition that the use of the

word "type" in an otherwise definite expression extends to render the expression indefinite.

The Examiner's rejection is based on factual error.

The word "type" is used but not defined in the specification.

The Examiner cites to a passage from the specification which nowhere defines the word "type." A definition conventionally includes an expression such as "The word ____ as used in the present specification and claims means ___ ." No such definition appears here. Appellants did not intend to act as their own lexicographers.

Instead, the appellants are simply using a universally understood term of art in the field of immunology in the same sense as the term is conventionally used in the art. In claim 20 and in the passage from the specification cited by the Examiner, "type" does not stand alone, but is modified by the adjective "immunological," and "immunological type" has a well defined meaning in the field of immunology, as the Board is no doubt aware.

Copenhaver does not support the Examiner's position. In Copenhaver the applicants used "type" in a completely different sense. In Copenhaver, the applicants used the term "Friedel Crafts type catalyst" and the Board found that appending "type" to the otherwise definite term "Friedel Crafts" rendered the term indefinite. Here, "type" is not appended to the term "immunological." Grammatically, it is used as a noun, rather than as an adjectival suffix as it is used in Copenhaver.

This rejection should be reversed.

2. Rejection Under 35 U.S.C. 102(e)/35 U.S.C. 103(a) Over Lin et al.

Appellants use the isocaudamer technique as part of their claimed process to generate literally thousands of sequences for evaluation as DNA vaccines. The prior art

cited by the Examiner, including Lin et al., discloses the use of the technique to prepare single, predefined sequences. This reflects a completely different mindset as to how to approach the problems inherent in trying to formulate an effective DNA vaccine.

During prosecution, the Examiner relied upon the English language abstract of a scientific publication appearing in Chinese in a Chinese scientific journal (cited as "Lin et al." in appellants' opening brief). However, in her Answer, the Examiner now relies upon an English language translation (dated December 16, 2009) of the Chinese document which she apparently procured in an attempt to shore up her position (hereinafter "the Lin translation"[1]. Consequently, there is good cause for appellants to make arguments in this reply brief that cannot be found in their opening brief: Basic fairness.

a) The Lin Translation Does Not Anticipate the Claims

In her Answer the Examiner contends that the Lin translation discloses all the elements of the claimed method "using implicit term(s) e.g. random." This is not true.

"Anticipation requires a showing that each limitation of a claim is found in a single reference, either expressly or inherently." Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006).

The Lin translation relates to the same general subject matter as does the instant patent application, using isocaudamer techniques to generate malaria vaccines, so it is not surprising that common terms appear in each. However, the Lin translation does not disclose, explicitly or implicitly, all of the steps of the claimed method, and thus cannot anticipate the present claims. Further, the Examiner makes no attempt to show that all

[1] The Examiner at times refers to the cited reference by the personal name of one of the authors, "Chengtao," rather than by the author's surname, "LIN" as would be conventional, and at other times as "the English translation."

the claim limitations are met by the reference. Instead, she only gives examples (Examiner's Answer, page 11, last paragraph) of a few instances in which the Lin translation uses experimental procedures which meet one of the limitations of the present claims. The Examiner has failed to provide a factual basis for her anticipation rejection. There is no reasonable basis to find appellants' presently claimed invention to be taught by the Lin translation either explicitly or inherently.

In particular, the Examiner states that the Lin translation teach that with isocaudamer tandem (bi-epitopes) linking of different kind of malaria are made, referencing step (b) of the independent claims and citing to Fig. 1, and paragraphs 2.1.2 and the second paragraph of the Discussion in the Lin translation. The Examiner further states that the isocaudamer linkage results in the multiplication of the single copy epitope (out of the multiple different length epitope derived from malaria antigen) and the tandem linkage of different kinds of epitopes. The Examiner further states that the tandem linkage of Lin is therefore random because the single copy of a fragment results in a library of multi-epitope clones of different length.

In fact, the Lin translation actually describes the synthesis of a single DNA vaccine containing three epitopes in specific quantities and in a specific sequence. The Lin translation discloses using the isocaudamers *BCl* I and *Bam*H I with clones of fragments 2 and 6 to give multiple copies of the clones. The multiple copies were then tandemized in a specific order ("2-8-6") to give a vaccine ("PU 286") containing a sequence of 16 copies of NKND (from fragment 2) and 4 copies of MSA (from fragment 8) separated by one copy of CST (fragment 8). The vaccine (recombinant plasmid) was digested to confirm insertion of the desired fragments and sequenced to confirm the structure.

It is unclear whether the Examiner is construing the Lin translation to expressly disclose the preparation of a library of DNA vaccines, or whether the Examiner considers this result to be an inherent result of the methods employed. In any event, it is not supported by the Results section of the Lin translation, which is, after all, headed "Construction of a Multivalent Recombinant DNA Vaccine" (emphasis added). PU 286 contains three epitopes, with two of the three epitopes being included in multiple copies. It is not a "bi-epitope" and consequently not even the limitations of even step (b) are met.

The Examiner also states that Lin discloses that the polyepitopes are derived from malaria antigen of different length fragments that result in different length sizes (ranges) as shown in the multiplication of a single clone, and that the English translation supports this at, e.g., paragraphs 2.1.1-2.1.2. As explained above, this is factually incorrect. Section 2.1.1 describes the synthesis of monoclones of individual synthetic fragments. The three types of clones produced each included only a single type of fragment, and each fragment contained only one epitope. None were "randomly combined bi-epitopes" are required by step (b). Section 2.1.2 describes the synthesis of a specific DNA vaccine, PU 286, containing three unique epitopes (no bi-epitopes here either).

The Examiner also contends that Lin teaches the cloning and subcloning (reiterative screening of the different clones) that results in a final single polyepitope effective in immunizing mice, which the Examiner contends to encompass the claim "steps i-h" (sic), citing to paragraphs 2.1.2 and 2.2 of the Lin translation. Not true. The Lin translation discloses making a single DNA vaccine with a specific sequence, PU 286, not a library of polyepitope chimeric genes. In paragraph 2.2, the Lin translation

discloses immunizing BALB/c mice with one DNA vaccine PU 286, and a control. Step (f) of claim 13 is not met.

Even if the Examiner were correct in her contention that the Lin translation discloses steps (b) and (h) of the claimed process, the Examiner fails to provide any factual basis for the many remaining process steps. For example, the Examiner makes no attempt to provide any factual support for the proposition that substeps of step (d), for example, are disclosed in the Lin translation.

In particular, it should be noted that the Lin translation reports only a high antibody response against the recombinant protein itself. The Lin translation did not report any response elicited by the DNA vaccine itself against the malaria parasite, which must be shown by immunofluorescence assay, and inhibiting *in vitro* growth of the parasite. Thus, the strategy reported by the Lin translation was far from achieving a successful multivalent vaccine against malaria.

The rejection under 35 U.S.C. 102(b) should be reversed.

b) The Lin Translation Does Not Render the Claimed Invention Obvious

The Examiner contends that the isocaudamers (i.e., different recognition sequences with compatible cohesive ends) would recognize or bind to the different clone fragments such that a pool (library) of clones of different length is created. The Examiner states that Paragraph 1.2 of the Lin translation shows that the fragments are of different length. The Examiner asserts that bi-epitopes combining the different length epitopes obviously produces different length epitopes, citing paragraph 2.1.2. The Examiner concludes that it would have been obvious to separate the different epitopes of different length into separate length ranges (sizes), as appellants recognize at page 10, lines 22-23, "one skilled in the art may set any desired length ranges." The

Examiner further concludes that it would also be within the ordinary skill in the art to ascertain termination of the reiterative step of recloning (rescreening) of a pool (library) of epitopes when the desire immunogenicity of the polyepitope is obtained.

Appellants respectfully submit that the Examiner's legal conclusion is based on factual error. Paragraph 1.2 of the Lin translation discloses four different nucleic acid fragments (three of which include epitopes and are isocaudamers) which are each synthesized for a specific purpose. The Examiner states that these three fragments yield a pool or library of bi-epitopes having different lengths, and that it would have been obvious to separate the different length bi-epitope into different length ranges. However, the Lin translation does not actually disclose preparation of a pool of bi-epitopes. On the contrary, each of the four fragments (fragments 1, 2, 6 and 8) is specially constructed for assembly in a specific order to form a DNA vaccine with a predetermined sequence. For example, the "purpose of fragment 1 is to introduce the start codon onto the carrier VR1012." The "duplicated stop codon TAATAA" is added to the end of fragment 6. "The GPBP sequence that is introduced in the antigen epitope ends of fragment 6 and fragment 8 plays the part of a partition sequence." The isocaudamer technique is used to assemble the fragments into one specific sequence,[2] and the structure of that sequence was confirmed: "further sequencing results proved that the sequence of the

[2] Although the isocaudamer technique can be used to randomly assemble epitopes into bi-epitopes, as disclosed in the present specification, Lin et al. does not disclose or suggest this use. Fig. 1 of the Lin translation, which illustrates the isocaudamer techniques, shows the use of the technique to purposefully assemble two epitopes into each of two different bi-epitopes differing sequences (AB and BA). There is nothing to suggest assembly of random pairs.

constructed polyvalent recombinant DNA vaccine is entirely correct" (Paragraph 2.1.2, final sentence). The use of the isocaudamer technique to form a pool of bi-epitopes is not disclosed, and not suggested in the Lin translation, but is rather pure speculation by the Examiner informed by appellants' own disclosure, as are the remaining process steps the Examiner argues to be obvious.

The Lin translation discloses a conventional, classical approach to forming a potential DNA vaccine. Pick a specific group of epitopes, and then assemble them in a predetermined sequence. There is nothing which would suggest or disclose to one of ordinary skill in the art that the isocaudamer technique could be used to produce randomly combined bi-epitopes by isocaudamer linkage (step b) of the process of independent claims 13 and 23. Furthermore, there is nothing to suggest any of the other steps of either independent claim.

Even if the process suggested by the Examiner were obvious in view of the Lin translation, it would not render obvious the presently claimed invention because the Examiner simply ignores several of the process steps required by the claims.

The Examiner makes no attempt to point to anything in the cited reference that would suggest step c) of claims 13 and 23 to one of ordinary skill in the art. Step c) requires the bi-epitopes to be randomly assembled into polyisotope chimeric genes with different lengths. However, in the Examiner's speculative interpretation of the Lin translation, it is the bi-epitopes themselves that have different lengths, and which are separated on the basis of those lengths and then tested for immunogenicity. Process step c) does not fit into the Examiners' hindsight-guided reconstruction of the present invention, so she just ignores it.

The Examiner cites the appellants' specification at page 10, lines 22-23 for the proposition that it would have been obvious to separate the bi-epitopes into different length ranges. However, this is simply taken totally out of context, and does not actually say what the Examiner contends. The statement is merely that "one skilled in the art may set any desired length ranges" but does suggest why any such ranges should be set in the first place, or why they should be separated. This is another factual error upon which the Examiner relies in making her rejection.

The Lin translation does not establish a *prima facie* case of obviousness, and the Examiner's rejection should be reversed.

3. Rejection Under 35 U.S.C. 103(a) Over Sette et al. or Fikes et al. in view of Richards et al. or Admitted Prior Art

To appellants' argument that Sette et al. does not disclose constructing polyepitope chimeric gene vaccines with a randomized the sequence of epitopes, the Examiner cites to Example 10 of Sette et al. Once again, the Examiner's rejection is based on factual error: Example 10 does not disclose randomization. Example 10 illustrates the procedure for the selection of peptide isotopes for construction an HPV (human papilloma virus) specific vaccine. The Example gives a set of principles for selecting an array of epitopes for inclusion in the vaccine composition. These include including epitopes that mimic immune responses observed to be correlated with HPV clearance (col. 58, lines 49-51); selecting epitopes derived from early and late stage HPV proteins (col. 58, lines 58-64); selecting sufficient supermotif-bearing peptides to give broad population coverage (col. 59, lines 1-7); generating the smallest possible peptide possible when constructing a polyepitopic composition (col. 60, lines 8-13). The Examiner expressly quotes the last principle, at col. 60, lines 14-21, which states that when sequences of multiple variants of the same target protein are available, the

potential peptide epitopes should be selected on the basis of their conservancy. Sette et al. give examples of criteria for conservancy, namely whether the entire sequence of an HLA class I binding peptide is conserved in a designated percentage of the individual sequences being evaluated for a specific protein antigen. There is no suggestion here that any such sequences be randomized. On the contrary, Sette et al. instructs one of ordinary skill in the art to construct a DNA vaccine with a specific set of sequences, using there criteria. The "multiple variants" of the target protein are not something that one of ordinary skill in the art constructs on purpose. Instead, sometimes these "are available," to the individual trying to construct the vaccine. This means that when variants of the specific protein component of the virus have already been identified, one of ordinary skill in the art should look to the extent to which specific sequences are conserved in the variants in picking a sequence to include in the gene vaccine.

The Examiner also quotes at some length from Example 11, in which Sette et al. disclose the construction of mini-gene multi-epitope DNA plasmids. In the specific example quoted by the Examiner, four pairs of oligonucleotides having partially overlapping sequences are combined and extended by PCR to form dimer products, which are gel-purified. The dimer products are then mixed and amplified using PCR, before being cloned into pCR-blunt. "[I]ndividual clones are screened by sequencing." One of ordinary skill in the art would understand that Example 11 relates to the construction of a minigene with a specific sequence, and that the sequences of each of the pairs of oligonucleotides are chosen so that the minigene produced has the target sequence. For example, while oligonucleotide A could include a short sequence complementary to a short sequence on oligonucleotide B, oligonucleotide B would include both a short sequence complementary to a short sequence of oligonucleotide A

and a short sequence complementary to a short sequence of oligonucleotide C. This approach is a common technique for constructing longer sequences by PCR, so that the abbreviated description in Example 11 is enabling for those skilled in the art. See, e.g. Ex parte Christian, Appeal No. 2009-006685 (BPAI December 20, 2009). Thus, the various epitopes in the minigene appear to a predefined sequence along the minigene, and there is no recognition by Sette et al. that the sequence in which they appear could affect their immunogenicity, or any attempt to produce a library in which the epitopes appear in random sequence along the minigene. Instead, Sette et al. sequence individual clones to confirm that a predetermined target sequence of epitopes has been achieved.

Further, there is no suggestion or disclosure that different length ranges of polyepitope minigenes be produced, that they should be separated, or that the length of the minigene could be related to its immunogenicity.

The Examiner makes no attempt to provide any genuine factual support for her contention that the many other steps required in appellants' independent claims are disclosed or even suggested by Sette et al.

Thus, there is no factual support for this rejection in Sette et al.

With respect to Fikes et al., the Examiner makes no attempt to respond to appellants' arguments, but merely refers the Board back to her comments regarding Sette et al. because appellants make similar arguments regarding Fikes et al. This is not sufficient. The Examiner has the initial burden of establishing a *prima facie* case that the claimed invention is obviousness under 35 U.S.C. § 103. In re Oetiker, 977 F.2d 1443, 1445 (Fed. Cir. 1992). The Examiner has the burden of identifying just where in Fikes et al. there is a disclosure or suggestion of the various steps of appellants'

independent claims that are not disclosed in the alternative secondary references (which disclose the isocaudamer technique). In her Answer, the Examiner makes no attempt to carry this burden.

Consequently, the Examiner has not made out a *prima facie* case of obviousness, and this rejection should be reversed by the Board.

Reversal of each of the rejections entered is again respectfully requested.

Respectfully submitted,

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